DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20852

JUL 02 2004

Our STN: BL 103928/0

Palatin Technologies, Incorporated
Attention: Kaushik Dave, Ph.D., R.Ph.
Vice President, Product Development
4-C Cedar Brook Drive
Cedar Brook Corporate Center
Cranbury, NJ 08512

Dear Dr. Dave:

We are issuing Department of Health and Human Services U.S. License No. 1588 to Palatin Technologies, Incorporated, Cranbury, NJ under the provisions of section 351(a) of the Public Health Service Act controlling the manufacture and sale of biological products. The license authorizes you to introduce or deliver for introduction into interstate commerce, those products for which your company has demonstrated compliance with establishment and product standards.

Under this license, you are authorized to manufacture the product Fanolesomab for the preparation of Technetium (99m Tc) Fanolesomab. Technetium (99m Tc) Fanolesomab is indicated for scintigraphic imaging of patients with equivocal signs and symptoms of appendicitis who are five years of age or older.

Under this license, you are approved to (b)(4) (b)(4) The final formulated product will be manufactured, filled, labeled, and packaged at Ben Venue Laboratories in Bedford, Ohio. You may label your product with the proprietary name NeutroSpec™ and will market it as a kit containing a 3 mL single-use vial of Fanolesomab and a 2 mL single-use ampule of Cenolate™ (Ascorbic Acid, USP).

The dating period for Fanolesomab shall be 24 months from the date of manufacture when stored at 2-8 °C. The date of manufacture shall be defined as the date of final sterile filtration of the formulated drug product. The dating period for your drug substance shall be 36 months when stored at -60 °C or below. The dating period for your intermediate drug product shall be 18 months when stored at -60 °C or below. The expiration date for the kit containing Fanolesomab and Cenolate™ shall be dependent on the shortest expiration date of either component.

You currently are not required to submit samples of future lots of Fanolesomab to the Center for Drug Evaluation and Research (CDER) for release by the Director, CDER, under 21 CFR 610.2. We will continue to monitor compliance with 21 CFR 610.1 requiring completion of tests for conformity with standards applicable to each product prior to release of each lot. You must submit information to your biologics license application for our review and written approval under 21 CFR 601.12 for any changes in the manufacturing, testing, packaging or labeling of Fanolesomab, or in the manufacturing facilities.

All applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred.

Your application was submitted without studies in pediatric patients less than 5 years of age. We are deferring submission of your studies for patients less than age 5 until May 31, 2007.

1. Your deferred pediatric study required under section 2 of the Pediatric Research Equity Act (PREA) is considered a required postmarketing study commitment. The status of this postmarketing study shall be reported annually according to 21 CFR 601.70. This commitment is listed below.

    a. Deferred pediatric study under PREA for the scintigraphic imaging of pediatric patients less than 5 years of age.

    b. Final Report Submission: May 31, 2007.

    Submit final study reports to this BLA. For administrative purposes, all submissions related to this pediatric postmarketing study commitment must be clearly designated "Required Pediatric Study Commitment".

If you believe that this drug qualifies for a waiver of the pediatric study requirement for patients less than 5 years of age, you should submit a request for a waiver with supporting information and documentation in accordance with the provisions of section 2 of the Pediatric Research Equity Act (PREA) by September 3, 2004. We will notify you within 120 days of receipt of your response whether a waiver is granted.

In addition, we acknowledge your written commitments as described in your letter of June 30, 2004, as outlined below:

Postmarketing Studies subject to reporting requirements of 21 CFR 601.70.

2. To conduct an open-label single-center pediatric dosimetry study to assess the safety, pharmacokinetics, and pharmacodynamics of Technetium (99m Tc) Fanolesomab in 12 to 18 pediatric patients, 5 to 16 years of age with equivocal signs and symptoms of appendicitis. Pediatric patients will be segregated into 3 year age groups (5 to 8, 9 to 12, and 13 to 16 years of age) and each age group will include four to six patients. Whole body images will be used to assess organ uptake and excretion of radioactivity. Pharmacokinetics of Technetium (99m Tc) Fanolesomab including blood pool clearance and clearance half-lives will be determined by drawing patient blood samples. The final study protocol will be submitted by September 15, 2004. Patient enrollment will be initiated by February 1, 2005, the last patient will be enrolled and the study will be completed by January 20, 2006, and the final study report will be submitted by June 25, 2006.

3. To conduct an open-label multicenter study to assess the safety and efficacy of Technetium (99m Tc) Fanolesomab in approximately 100 patients with equivocal signs and symptoms of appendicitis and who have polymorphonuclear leukocyte (PMN) counts at or below the lower limit of normal, neutropenia, ($n \geq 45$) or at low normal levels ($\leq 3{,}000/mm^3$) at the time of enrollment in the study. The final study protocol will be submitted by September 15, 2004. Patient enrollment will be initiated by February 1, 2005, the last patient will be enrolled and the study will be completed by January 15, 2006, and the final study report will be submitted by June 15, 2006.

4. To provide data supporting a validated quantitative immunogenicity assay for the detection of a patient immune response (anti-drug binding antibodies) to Technetium (99m Tc) Fanolesomab by January 31, 2006.

5. To conduct a study on the immunogenicity of Technetium (99m Tc) Fanolesomab in patients using a validated assay (b)(4). The method of storage of archived patient serum samples from completed clinical studies will be assessed to determine the suitability of using these samples in the validated quantitative immunogenicity assay. If these samples are unsuitable for immunogenicity testing purposes, then serum samples will be collected from ongoing and/or additional clinical studies. The sample size of the study will be sufficient to exclude an incidence of anti-drug antibody development $>10\%$. The study protocol will be submitted by October 31, 2005, the study will be initiated January 31, 2006, and will be completed by December 31, 2006. The final study report will be submitted June 30, 2007.

6. To conduct a study to determine whether human anti mouse antibodies (HAMA), detected with a validated assay (b)(4), interfere with diagnostic *in vitro* assays that utilize murine antibodies, and to determine the relationship between levels of HAMA and interference. The study will be completed by June 30, 2006. The final study report will be submitted by December 31, 2006.

Postmarketing Studies not subject to reporting requirements of 21 CFR 601.70.

7. To evaluate the in-process, release and shelf-life specifications for Fanolesomab drug substance, intermediate drug product, and drug product on a yearly basis to reflect increased manufacturing experiences. The cumulative data and analysis for product manufactured up to and including 2004 will be provided in the July 2004 to July 2005 Annual Report to be submitted by September 30, 2005. Specifications will be re-evaluated on a yearly basis and the cumulative data and analysis for product manufactured up to and including 2010 will be provided annually.

8. To improve control of the HL-60 and Raji cells used in the potency assays by collecting stability data, validating new methods, and setting new specifications as specified below:

   a. To develop and validate a saturation binding method and to evaluate the relationship between the numbers of binding sites as determined by saturation binding and the Lindmo method (IRF) values using a reference lot of antibody.

   b. To establish acceptance specifications and an expiry period for the HL-60 and Raji cells that include limits for the number of binding sites/cell, and IRF values.

   c. To submit updated protocols for qualification of the new HL-60 and Raji cell banks based on new information acquired from the above studies.

   Method validation reports, updated specifications, and updated cell banking qualification protocols will be submitted by December 31, 2005. Stability data and expiration dating will be submitted by June 30, 2006.

9. To conduct a study and to provide the data validating the shipping of Fanolesomab samples for release testing at Palatin, (b)(4) (b)(4) to Palatin Technologies in Cranbury, New Jersey and of your drug product from Ben Venue Laboratories in Bedford, Ohio to Palatin Technologies in Cranbury, New Jersey. Additionally, data supporting your ability to maintain final drug product at a temperature of 2-8° C when shipped from Ben Venue Laboratories to your distributor during elevated outside ambient temperatures (e.g., summer months) should be submitted for three separate shipments of NeutroSpec™ kits. The study will be complete June 30, 2005, and the final study report will be submitted September 30, 2005.

10. To provide stability data for the Fanolesomab conformance lots for the requested expiration dating of 36 months at storage temperature of ≤ -60 °C for drug substance, 18 months at a storage temperature of ≤ -60 °C for intermediate drug product and 24 months at a storage temperature of 2-8 °C for drug product. Yearly updates to the stability data will be submitted in the Annual Report. The stability study will be completed by March 31, 2007, and the final study report will be submitted by August 31, 2007.

11. To submit the post-approval stability protocol for Fanolesomab. The protocol should identify situations when Fanolesomab will be put on stability, as well as include the following real time, long term stability studies:

    a. One drug substance lot manufactured per year for every year that drug substance is manufactured.

    b. One intermediate drug product lot manufactured per year for every year that intermediate drug product is manufactured.

    c. One drug product lot manufactured per year for every year that drug product is manufactured.

    The final protocol will be submitted September 30, 2004.

12. To submit the final validation report on the new (b)(4) [redacted] assay currently being developed. The final validation report will be submitted by December 31, 2004.

13. To perform genetic stability testing on a production lot of Fanolesomab at the limit of *in vitro* cell age. Peptide mapping results will be verified by comparing the nucleotide sequence of Fanolesomab in the master cell bank and in aged cells. Final testing will be completed by March 31, 2006, and the final study report will be submitted by June 30, 2006.

14. To develop and to validate assays, and to set quantitative limits for Fanolesomab carbohydrate composition prior to qualification of the next Fanolesomab reference standard. Assay validation will be completed by June 30, 2005, and the final study report will be submitted by October 31, 2005.

15. To develop and to validate assays, and to set quantitative limits for IgM hexamer and J chain prior to qualification of the next Fanolesomab reference standard. The assay validation will be completed by June 30, 2005, and the final study report will be submitted by December 31, 2005.

We request that you submit clinical protocols to your INDs, with a cross-reference letter to this biologics license application (BLA), STN BL 103928. Submit nonclinical and chemistry, manufacturing, and controls protocols and all study final reports to your BLA, STN BL 103928. Please use the following designators to label prominently all submissions, including supplements, relating to these postmarketing study commitments as appropriate:

- **Postmarketing Study Protocol**
- **Postmarketing Study Final Report**
- **Postmarketing Study Correspondence**
- **Annual Report on Postmarketing Studies**

For each postmarketing study subject to the reporting requirements of 21 CFR 601.70, you must describe the status in an annual report on postmarketing studies for this product. The status report for each study should include:

- information to identify and describe the postmarketing commitment,
- the original schedule for the commitment,
- the status of the commitment (i.e. pending, ongoing, delayed, terminated, or submitted), and
- an explanation of the status including, for clinical studies, the patient accrual rate (i.e. number enrolled to date and the total planned enrollment).

As described in 21 CFR 601.70(e), we may publically disclose information regarding these postmarketing studies on our Web site (http://www.fda.gov/cder/pmc/default.htm). Please refer to the April 2001 Draft Guidance for Industry: Reports on the Status of Postmarketing Studies – Implementation of Section 130 of the Food and Drug Administration Modernization Act of 1997 (see http://www.fda.gov/cber/gdlns/post040401.htm) for further information.
END SECTION

You must submit adverse experience reports under the adverse experience reporting requirements for licensed biological products (21 CFR 600.80). You should submit postmarketing adverse experience reports to the Central Document Room, Center for Drug Evaluation and Research, Food and Drug Administration, 5901-B Ammendale Road, Beltsville, MD 20705-1266. Prominently identify all adverse experience reports as described in 21 CFR 600.80.

The MedWatch-to-Manufacturer Program provides manufacturers with copies of serious adverse event reports that are received directly by the FDA. New molecular entities and important new biologics qualify for inclusion for three years after approval. Your firm is eligible to receive copies of reports for this product. To participate in the program, please see the enrollment instructions and program description details at www.fda.gov/medwatch/report/mmp.htm.

You must submit distribution reports under the distribution reporting requirements for licensed biological products (21 CFR 600.81). You should submit distribution reports to CBER Document Control Center, Attn: Office of Therapeutics Research and Review, Suite 200N (HFM-99), 1401 Rockville Pike, Rockville, MD 20852-1448

You must submit reports of biological product deviations under 21 CFR 600.14. You promptly should identify and investigate all manufacturing deviations, including those associated with processing, testing, packing, labeling, storage, holding and distribution. If the deviation involves a distributed product, may affect the safety, purity, or potency of the product, and meets the other criteria in the regulation, you must submit a report on Form FDA-3486 to the Division of Compliance Risk Management and Surveillance (HFD-330), Center for Drug Evaluation and Research, Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857.

Please submit all final printed labeling at the time of use and include implementation information on FDA Form 356h. Please provide a PDF-format electronic copy as well as original paper copies (ten for circulars and five for other labels). In addition, you may wish to submit draft copies of the proposed introductory advertising and promotional labeling with a cover letter requesting advisory comments to the Division of Drug Marketing, Advertising and Communication (HFD-42), Center for Drug Evaluation and Research, Food and Drug Administration, 5600 Fishers Lane/Room 8B45, Rockville, MD 20857. Final printed advertising and promotional labeling should be submitted at the time of initial dissemination, accompanied by a FDA Form 2253.

All promotional claims must be consistent with and not contrary to approved labeling. You should not make a comparative promotional claim or claim of superiority over other products unless you have substantial evidence to support that claim.

The regulatory responsibility for review and continuing oversight for this product transferred from the Center for Biologics Evaluation and Research to the Center for Drug Evaluation and Research effective June 30, 2003. For further information about the transfer, please see http://www.fda.gov/cder/biologics/default.htm. Until further notice, however, all correspondence, except as provided elsewhere in this letter, should continue to be addressed to:

CBER Document Control Center
Attn: Office of Therapeutics Research and Review
Suite 200N (HFM-99)
1401 Rockville Pike
Rockville, Maryland 20852-1448

Sincerely,

(b)(6)

Karen D. Weiss, M.D.
Director
Office of Drug Evaluation VI
Center for Drug Evaluation and Research

NEUTROSPEC™
Kit for the Preparation of Technetium (99m Tc) fanolesomab

Diagnostic Radiopharmaceutical
For intravenous use only
Rx ONLY
CONTAINS SODIUM HYDROSULFITE

DESCRIPTION

NeutroSpec™ [Kit for the Preparation of Technetium (99m Tc) fanolesomab] is a radiodiagnostic agent consisting of a murine IgM monoclonal antibody, formulated to be labeled with technetium Tc 99m. Each NeutroSpec™ kit contains all the excipients needed to reconstitute and to radiolabel this imaging agent with sodium pertechnetate Tc 99m Injection, USP. The murine monoclonal antibody fanolesomab is produced in suspension culture of hybridoma cells. NeutroSpec™ [Technetium (99m Tc) fanolesomab] is an *in vivo* diagnostic radiopharmaceutical that can be visualized by nuclear medicine instrumentation.

Each NeutroSpec™ kit contains a single use vial of fanolesomab as a sterile, non-pyrogenic, lyophilized mixture of 0.25 mg fanolesomab; 12.5 mg maltose monohydrate; 0.522 mg sodium potassium tartrate tetrahydrate, USP; 0.221 mg succinic acid; 54 mcg stannous tartrate (minimum stannous 7 mcg; maximum total stannous and stannic tin 24 mcg); 28 mcg glycine, USP; and 9.3 mcg disodium edetate dihydrate, USP. The lyophilized powder contains no preservatives and has no US standard of potency. When sterile, pyrogen-free sodium pertechnetate Tc 99m Injection, USP in isotonic saline (no preservatives) is added to the single use fanolesomab vial, a Tc 99m complex of fanolesomab is formed with an approximate pH of 6.2.

Physical Characteristics of Technetium Tc 99m

Technetium 99m decays by isomeric transition with a physical half-life of 6.02 hours. The photon that is useful for imaging studies is listed in **Table 1**.

Table 1. Principal radiation emission data for technetium Tc 99m

Radiation	Mean Percent per Disintegration	Mean Energy (keV)
Gamma-2	89.07	140.5

External Radiation

The specific gamma-ray constant for technetium Tc 99m is 5.4 $\mu C \cdot kg^{-1} \cdot MBq^{-1} \cdot h^{-1}$ (0.78 R/mCi·h) at 1 cm. The first half-value thickness of lead for Tc 99m is 0.017 cm. A range of values for the relative attenuation of the radiation emitted by this radionuclide that results from the interposition of various thicknesses of lead is shown in **Table 2**. For example, the use of a 0.25 cm thickness of lead will decrease the external radiation exposure by a factor of 1,000.

Table 2. Radiation attenuation by lead shielding

Lead Shield Thickness (cm)	Coefficient of Attenuation
0.017	0.5
0.08	0.1
0.16	0.01
0.25	0.001
0.33	0.0001

To correct for physical decay of this radionuclide, the fractions that remain at selected time intervals after the time of calibration are shown in **Table 3.**

Table 3. Physical decay chart—technetium Tc 99m half-life 6.02 hours

Hours	Fraction Remaining	Hours	Fraction Remaining
0*	1.00	7	0.45
1	0.89	8	0.40
2	0.79	9	0.36
3	0.71	10	0.32
4	0.63	11	0.28
5	0.56	12	0.25
6	0.50	18	0.13

*Calibration Time (time of preparation)

CLINICAL PHARMACOLOGY

Pharmacodynamics

Fanolesomab is directed against the carbohydrate moiety 3-fucosyl-*N*-acetyllactosamine that defines the cluster of differentiation 15 (CD15) antigen. NeutroSpec™ [Technetium (99m Tc) fanolesomab] radiolabels human white blood cells and myeloid precursors. The CD15 antigen is expressed on the surface of polymorphonuclear neutrophils (PMNs), eosinophils and monocytes. Monocytes and eosinophils constitute approximately 5% of circulating leukocytes; therefore, most of the circulating blood cellular activity resides on PMNs. In blood cell fractions isolated from healthy volunteers who had received NeutroSpec™, radioactivity was associated with PMNs (25%) or plasma (72%) when measured one hour after injection. The binding of fanolesomab to its antigenic sites on human PMNs has an apparent $K_d = 1.6 \times 10^{-11}$ M.
Cross-reactivity studies indicate the presence of CD15 antigenic sites on many human tissues.

Pharmacokinetics

In a study of 10 healthy volunteers, following intravenous injection of NeutroSpec™, blood concentrations of radioactivity decreased rapidly with an initial half-life of 0.3 hours and a second phase half-life of approximately eight hours. Whole-body scintigraphy at two hours post-injection indicated that the liver had the highest

radioactivity uptake and retention (50% of the injected dose), followed by the kidney, spleen and red marrow. Over the 26–33 hours after injection, 38% of the injected dose of radioactivity was recovered in urine.

CLINICAL STUDIES

A multicenter, single-arm study evaluated 200 patients (5 to 86 years of age) with equivocal signs and symptoms of appendicitis defined as absence of one or more of the following: periumbilical pain migrating to right lower quadrant (RLQ), gradual onset of pain, increasing intensity of pain over time, pain aggravated by movement and coughing, McBurney's point tenderness, referred tenderness to RLQ with palpation in other quadrants, abdominal muscular spasm with RLQ tenderness, temperature > 101^0 F, white blood cell count > 10,500/mm^3. Readers blinded to clinical information (except for age, gender and body habitus) assessed the diagnosis of appendicitis by NeutroSpec™ imaging. The diagnosis by the blinded readers was compared with a final clinical diagnosis based upon a surgical pathology report (in cases that proceeded to appendectomy) or upon two weeks of follow-up (in cases without surgical intervention). The study investigators had access to other diagnostic modalities (e.g., CT scan and ultrasound) and were instructed not to rely on NeutroSpec™ imaging for their diagnosis of appendicitis. Appendicitis prevalence in this study was 30%. The image evaluation was limited to the assessment of the planar images performed in specified projections at defined time points and single photon emission tomography was not used to assess performance in this study.

The performance rates for the diagnosis of appendicitis by the blinded readers and by the clinical investigators are shown in **Table 4.**

Table 4. Diagnostic performance of NeutroSpec™

Evaluation	Performance Rates (n=200)	
	Blinded Readers percentages (95%CI)	Study Investigators percentages(95%CI)
Sensitivity	75 (62, 85)	91 (80, 97)
Specificity	93 (87, 97)	86 (79, 91)
Accuracy	87 (82, 92)	87 (81, 91)
Positive Predictive Value	82 (69, 91)	74 (62, 84)
Negative Predictive Value	90 (84, 94)	96 (90, 99)

In a supportive single-arm, two-center study of the detection of appendicitis in 56 patients of whom 50% had a final diagnosis of appendicitis, the diagnostic performance of NeutroSpec™ was similar to the performance observed in the larger study.

Other intra-abdominal conditions

Among 30 study patients with other types of intra-abdominal infection (surgical and non-surgical), 13 scintigrams were read as positive for appendicitis.

INDICATIONS AND USAGE

NeutroSpec™ [Technetium (99m Tc) fanolesomab] is indicated for scintigraphic imaging of patients with equivocal signs and symptoms of appendicitis who are five years of age or older.

CONTRAINDICATIONS

NeutroSpec™ should not be administered to patients who are hypersensitive to any murine proteins or other component of the product.

WARNINGS

Hypersensitivity Reactions

Allergic reactions, including anaphylaxis, can occur in patients who receive murine antibodies such as fanolesomab.

Cenolate™ Ascorbic Acid, USP injection (diluent) contains sodium hydrosulfite, a sulfite that may cause allergic reactions, including anaphylaxis. Serious hypersensitivity reactions were not observed in the 523 patients who received NeutroSpec™ in the clinical studies. Emergency resuscitation personnel and equipment for the treatment of hypersensitivity reactions should be immediately available during administration of this agent.

PRECAUTIONS

Repeat Administration

NeutroSpec™ has not been studied in repeat administration to patients. Murine monoclonal antibodies are frequently immunogenic. The development of human anti-mouse antibodies (HAMA) can alter the pharmacokinetics, biodistribution, safety, and imaging performance properties of the administered agent.

Use in Patients with Neutropenia

The biodistribution and the imaging performance of NeutroSpec™ in neutropenic patients have not been studied. NeutroSpec™ induces transient neutropenia and a downward shift in white blood cell counts. (See **ADVERSE REACTIONS Laboratory Values)**. The safety and effectiveness of NeutroSpec™ in patients with neutropenia have not been established.

General Use and Handling

NeutroSpec™ [Technetium (99m Tc) fanolesomab], like other radioactive medical products, must be handled with care and appropriate safety measures should be used to minimize radiation exposure to clinical personnel. Care should also be taken to minimize radiation exposure to the patient consistent with proper patient management. Radiopharmaceuticals should be used by or under the control of personnel who are qualified by specific training and experience in the safe use and handling of radionuclides, and whose experience and training have been approved by the appropriate governmental agency authorized to license the use of radionuclides.

Information for patients

Murine monoclonal antibodies such as fanolesomab are foreign proteins and their administration can induce hypersensitivity reactions. Patients should be informed that the use of this product could affect their future use of other murine based products, and should be advised to discuss prior use of murine antibody based products with their health care provider.

To minimize the radiation-absorbed dose to the bladder, adequate hydration should be encouraged to permit frequent voiding during the first few hours after injection. To help protect themselves and others in their environment, patients should take the following precautions for 12 hours after injection. Whenever possible, a toilet should be used, rather than a urinal and the toilet should be flushed several times after each use. Spilled urine should be cleaned up completely. After each voiding or fecal elimination, patients should thoroughly wash their hands. If blood, urine or feces soil clothing, the clothing should be washed separately.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Studies have not been conducted to evaluate carcinogenic potential, mutagenic potential, or effects on fertility.

Pregnancy

Pregnancy Category C. Animal reproductive studies have not been conducted with NeutroSpec™. It is also not known whether NeutroSpec™ can cause fetal harm when administered to a pregnant woman or can affect reproductive capacity. NeutroSpec™ should not be used during pregnancy unless the potential benefit to the patient justifies the potential risk to the fetus.

Nursing Mothers

It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when NeutroSpec™ is administered to a nursing woman. Whenever possible, infant formula should be substituted for breast milk until the radioactivity has cleared from the body of the nursing woman.

Pediatric Use

In clinical studies of NeutroSpec™, 29 (5%) patients were 5–11 years old and 32 (6%) were 12–16 years old. No overall differences in safety or effectiveness were observed between these patients and patients in other age brackets, however, this number of patients is too few to exclude differences.

Geriatric Use

In clinical studies of NeutroSpec™, 64 (12%) patients were 65 years or older. No overall differences in safety or effectiveness were observed between these patients and younger patients, but this number of patients is too few to exclude differences.

ADVERSE REACTIONS

The data described below reflect exposure to NeutroSpec™ in 523 patients and normal volunteers receiving a mean antibody dose of 121 mcg (33–250 mcg) and a mean

radioactive dose of 15 mCi (1-33 mCi). The median patient age was 35 years (5-91 years); 53% of patients were women and 61% of patients were Caucasians.

Two patients enrolled in studies of post surgical infection or abscess had serious adverse events associated with fatality (hypotension and worsening of sepsis). Underlying medical conditions may have also contributed to the fatality and the relationship of the fatality to NeutroSpec™ cannot be determined.

Overall, 49 adverse events occurred in 37 (7%) of the 523 patients exposed to NeutroSpec™. Four of these events were classified as severe (hypotension, worsening of sepsis, chest pressure and decreased SaO_2, pain). The most frequently reported adverse events were flushing (n=10, 2%) and dyspnea (n=5, 1%). Other less common adverse events (< 1%) included syncope, dizziness, hypotension, chest pressure, paresthesia, nausea, injection site burning/erythema, pain, and headache.

Because clinical trials are conducted under widely varying controlled conditions, adverse reaction rates observed in clinical trials of a drug cannot be directly compared with rates in the clinical trials of another drug, and may not reflect the rates observed in practice. The adverse reaction information from clinical trials does, however, provide a basis for identifying the adverse events that appear to be related to drug use and for approximating rates.

Laboratory Test Values

NeutroSpec™ induced transient decreases in neutrophil counts in a study of 10 healthy volunteers. Neutrophil counts began to decrease within 3 to 5 minutes post-injection and returned to pre-injection values within four hours. Downward shifts in neutrophil counts have been observed in 18% of patients (28/151). Three of 284 patients were observed to develop transient elevations of AST and ALT after NeutroSpec™ administration.

Immunogenicity

The incidence of antibody development in patients receiving NeutroSpec™ has not been adequately determined because the assay was not directly quantitative and its ability to detect low titers could not be assured. Human anti-mouse antibody (HAMA) response following a single NeutroSpec™ administration was evaluated in a total of 54 patients 3-16 weeks post injection. None of the patients had a positive HAMA response. In 30 healthy volunteers who were exposed to two administrations of fanolesomab separated by two weeks, fanolesomab induced HAMA response in five volunteers.

Immunogenicity data are highly dependent on the sensitivity and specificity of the assay. Additionally, the observed incidence of antibody positivity in an assay may be influenced by several factors, including sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, comparison of the incidence of antibodies to NeutroSpec™ with the incidence of antibodies to other products may be misleading.

OVERDOSAGE

There is no experience with overdosage in clinical trials.

DOSAGE AND ADMINISTRATION

Adults

To prepare NeutroSpec™ the reaction vial containing fanolesomab is reconstituted with sodium pertechnetate Tc 99m Injection, USP solution prior to use. (See **INSTRUCTIONS FOR PREPARATION**).

Fanolesomab is not intended for direct administration to the patient without reconstitution and labeling with sodium pertechnetate Tc 99m Injection, USP. NeutroSpec™ [Technetium (99m Tc) fanolesomab] is intended for a single intravenous (IV) administration through an intravenous access that has been demonstrated to be patent, e.g., butterfly, running IV line, or equivalent injection system to assure that no dose infiltration occurs. Following administration, flush the injection line with an appropriate volume of saline to assure administration of the total dose.

For imaging, 75 to 125 mcg of fanolesomab is labeled with 10 to 20 mCi (370 to 740 MBq) and administered as a single dose of NeutroSpec™.

Planar imaging should be performed using a large field of view camera fitted with a low-energy, parallel-hole, high-resolution collimator. The camera should be positioned so that the lower edge of the liver is at the upper end of the field of view at the midline of the patient.

Dynamic image acquisition over the lower abdomen should begin at the time of injection and consist of 10 sequential four-minute images. Following dynamic image acquisition, the patient should ambulate for approximately 10 to 15 minutes and void. Static planar images should then be collected, including supine anterior, posterior, 10–25 degree RAO and LAO views of the lower abdomen, followed by a standing anterior image of the lower abdomen. After the camera has been positioned (as described above), it is recommended that a total of one million counts be collected for the anterior supine image. All remaining images should be collected for the same duration of time required for the anterior supine image.

Children (Five years and older)

NeutroSpec™ is administered in a single dose of 0.21 mCi/kg to a maximum of 20 mCi. Recommended imaging times and procedures are the same as for adults.

Dose adjustment has not been established in patients with renal insufficiency, in geriatric patients or in pediatric patients under five years of age.

Image Interpretation

The biodistribution of the NeutroSpec™ radiopharmaceutical is imaged in the blood pool, reticuloendothelial system (liver, spleen, bone marrow), and urinary excretion organs (kidneys and urinary tract). Imaging of the uterus has been noted, consistent with blood pool activity of NeutroSpec™.

In the 200-patient clinical trial (see CLINICAL STUDIES), based on the average of the three blinded reader interpretations, 75% of the 59 true positive cases of appendicitis were identified (range 66-81%).

Among those with a blinded diagnosis of appendicitis, 76% displayed uptake of radiotracer activity in the appendix within 30 minutes following injection and 98% did so by 60 minutes following injection.

In the trial the acquisition of image collection was performed for a 90 minute period. The image finding of a persistent or intensifying uptake in the right lower quadrant (appendix zone) that is seen before the completion of the entire imaging sequence may be considered a positive study, and imaging may be terminated at this time. In the case of a negative image finding at 30 and 60 minutes, collection to 90 minutes is recommended prior to termination of the study.

A diagnostic abnormality is characterized by the presence of an irregular, asymmetric uptake of radiotracer localized in the right lower quadrant of the abdomen. The abnormal localization of radiotracer remains constant or increases in intensity in follow up imaging.

RADIATION DOSIMETRY

Based on human data, the absorbed radiation dose to an average human adult (70 kg) from an intravenous injection of NeutroSpec™ is listed in **Table 5**. The values were calculated using the Standard Medical Internal Radiation Dosimetry (MIRD) method. The values are listed as rad/mCi and mGy/MBq and assume urinary bladder emptying at 4.8 hours. Radiation absorbed dose estimates for children are given in **Table 6.**

Table 5. Absorbed radiation dose in adults (NeutroSpec™)

Target Organ	rad/mCi	mGy/MBq
Spleen	0.23	0.062
Kidneys	0.19	0.051
Liver	0.18	0.048
Urinary Bladder Wall	0.12	0.032
Heart	0.061	0.017
Gallbladder	0.056	0.015
Upper Large Intestine Wall	0.051	0.014
Adrenal Glands	0.044	0.012
Lungs	0.043	0.012
Thyroid Gland	0.042	0.011
Red Marrow	0.038	0.010
Lower Large Intestine Wall	0.034	0.0091
Bone Surface	0.031	0.0083
Brain	0.0052	0.0014
Testes / Ovaries	0.0039 / 0.019	0.0010 / 0.0052
Total Body	0.019	0.0050

Dose calculations were performed using the standard MIRD method (MIRD Pamphlet No. 1 rev., Soc. Nucl. Med., 1976). Effective dose equivalent was calculated in accordance with ICRP 53 (Ann. ICRP 18, 1-4, 1988) and gave a value of 0.018 mSv/MBq (0.068 rem/mCi).

Table 6. Estimated absorbed radiation dose for a five-year old child

Target Organ	rad/mCi	mGy/MBq
Spleen	0.70	0.19
Kidneys	0.43	0.11
Liver	0.41	0.11
Urinary Bladder Wall	0.27	0.072
Upper Large Intestine Wall	0.21	0.056
Thyroid Gland	0.19	0.052
Lower Large Intestine Wall	0.16	0.042
Heart	0.15	0.041
Gallbladder	0.13	0.036
Red Marrow	0.11	0.030
Lungs	0.11	0.028
Adrenal Glands	0.095	0.026
Bone Surface	0.085	0.023
Testes / Ovaries	0.019 / 0.059	0.0052 / 0.016
Brain	0.0075	0.0020
Total Body	0.049	0.013

Dose calculations were performed using the standard MIRD method based upon biodistribution studies conducted in adults. Effective dose equivalent was calculated in accordance with ICRP 53 and gave a value of 0.047 mSv/MBq (0.17 rem/mCi).

INSTRUCTIONS FOR THE PREPARATION OF NEUTROSPEC™

USE ASEPTIC TECHNIQUE THROUGHOUT

The user should wear waterproof gloves during the entire procedure and while withdrawing the patient dose from the NeutroSpec™ vial.

Transfer Sodium Pertechnetate Tc 99m Injection, USP with an adequately shielded, sterile syringe.

Adequate shielding should be maintained at all times until the preparation is administered to the patient, disposed of in an approved manner, or allowed to decay to background levels. A shielded, sterile syringe should be used to withdraw and inject the labeled preparation.

Before reconstituting a vial, it should be inspected for cracks and any indication that the integrity of the vacuum seal has been lost. The material should not be used if integrity of the vacuum seal has been lost. After reconstitution, examine the vial contents for particulates and discoloration prior to injection. The material should not be used if particulates or discoloration are observed.

The dose should be injected via an indwelling catheter, butterfly, or equivalent injection system to assure that no dose infiltration occurs. Following administration, flush the injection line with an appropriate volume of saline to assure administration of the total dose.

Labeling and Preparation of NeutroSpec™

1. Required Materials, Not Supplied within the NeutroSpec™ kit:

   a. **Sodium Pertechnetate Tc-99m, USP, oxidant-free**
   b. **ITLC-SG Strips, Heat Treated**
   c. **Methyl Ethyl Ketone (MEK)**
   d. **Developing Chambers - 50 mL disposable tubes**
   e. **Pipettors and tips**
   f. **Forceps**
   g. **Gamma Counter**
   h. **Dose Calibrator**
   i. **Sodium Chloride for Injection, USP**
   j. **Alcohol (or Germicidal)**
   k. **Lead Shield**
   l. **1 mL Sterile Syringes**
   m. **Water Bath stabilized at 37±1° C**

2. Remove a fanolesomab reaction vial from refrigerated storage (2 to 8° C) and allow it to come to room temperature (usually 5 to 10 minutes). NOTE: Keep Cenolate ampule refrigerated and protected from light until needed (Step 5).

3. Swab the rubber stopper of the fanolesomab reaction vial with an appropriate antiseptic and allow the stopper to dry.

4. Aseptically add 20 to 40 mCi (740 to 1480 MBq) Sodium Pertechnetate Tc 99m Injection, USP in 0.20 to 0.35 mL generator eluate. Gently swirl (**Do not shake**) the vial until the lyophilized product is completely dissolved, ensuring the vial is not inverted.

   Cautionary Notes:

   - **Use only eluate from a technetium Tc 99m generator that was previously eluted within the last 24 hours.**
   - **Technetium 99m eluate which is more than 8 hours old from the time of elution should NOT be used.**
   - **The amount of Sodium Pertechnetate Tc 99m Injection, USP used to reconstitute the reaction vial should be determined based on the desired radioactive dose and the estimated time of use.**
   - **If Sodium Pertechnetate Tc 99m Injection, USP must be diluted prior to kit reconstitution, only sterile sodium chloride for injection, USP, (without preservatives) should be used.**

5. Incubate at 37° C for 30 minutes. (Shorter incubation times may result in inadequate labeling.)

6. Aseptically add sufficient Cenolate™ [Ascorbic Acid Injection, USP (500 mg/mL)] to make the final preparation volume up to 1 mL.

Note: Further dilution is not recommended.

7. Assay the product in a suitable calibrator and record the time, date of preparation and the activity of NeutroSpec™ onto the string tag label and attach to lead dispensing shield ("pig").

8. Each patient should receive a dose of 10-20 mCi of NeutroSpec™ (the final reconstituted product).

9. Discard vials, needles and syringes in accordance with local, state, and federal regulations governing radioactive and biohazardous waste.

Recommended Method for Radiochemical Purity Testing

1. After addition of Cenolate™ (Ascorbic Acid Injection, USP) aseptically withdraw approximately 10 µL of the final reconstituted product for Quality Control (QC) testing. Care should be taken not to introduce air into the vial. Use of a shielded 0.5 - 1.0 cc syringe with a 25 or 27 gauge needle is recommended.

2. Apply 1 - 5 µL (a drop that has not completely formed on the tip of a 25 - 27 gauge needle) of NeutroSpec™ 2 cm (origin) from the bottom of an ITLC-SG 1.5 x 10 cm strip and allow the solution to absorb into the strip (approximately 5 seconds).

3. Immediately place the strip, origin side down, in a development chamber containing 4 mL methyl ethyl ketone (MEK).

4. Allow the strip to develop until the solvent front is within 0.5 cm of the top of the strip (3 - 5 minutes).

5. Remove the strip using forceps and allow to dry.

6. Cut the strip at the 4 cm mark, place each piece in a separate counting tube and measure the radioactivity associated with each piece.

7. Calculate the % Free Technetium Tc 99m Pertechnetate as follows:

$$\% \text{ Free Pertechnetate} = \frac{\text{Radioactivity in Solvent Front Piece}}{\text{Total Radioactivity in Strip}} \times 100\%$$

Note: The product should only be used if the percentage of Free Technetium Tc 99m Pertechnetate is ≤ 10%.

HOW SUPPLIED

NeutroSpec™ Kit for the Preparation of Technetium (99m Tc) fanolesomab

The NeutroSpec™ kit contains five individual kits each containing:

One	3 mL single use vial of fanolesomab as a sterile, non-pyrogenic, lyophilized mixture of 0.25 mg fanolesomab; 12.5 mg maltose monohydrate; 0.522 mg sodium potassium tartrate tetrahydrate, USP; 0.221 mg succinic acid; 54 mcg stannous tartrate (minimum stannous 7 mcg; maximum total stannous and stannic tin 24 mcg); 28 mcg glycine, USP; and 9.3 mcg disodium edetate dihydrate, USP. The lyophilized powder contains no preservatives and has no US standard of potency.
One	2 mL ampule Cenolate™ [Ascorbic Acid Injection, USP (500 mg/mL)]
One	NeutroSpec™ Package Insert
One	String tag label for NeutroSpec™ vials (reconstituted product)

STORAGE

Refrigerate the lyophilized NeutroSpec™ kits at 2 to 8° C (36 to 46° F). After labeling with Sodium Pertechnetate Tc 99m Injection, USP and addition of Cenolate™ (Ascorbic Acid injection, USP) the vial should be kept at room temperature, 15 to 25° C (46 to 77° F) and used within **six** hours. Use appropriate radiation shielding.

This reagent kit is approved for distribution to persons licensed by the U.S. Nuclear Regulatory Commission to use byproduct material identified in 10 CFR 35.200 or under an equivalent license issued by an Agreement State.

NeutroSpec™ is manufactured for Palatin Technologies, Inc., Cranbury, NJ 08512 by Ben Venue Laboratories, Inc., Bedford, OH 44146

U.S. Patent X,XXX,XXX
US license number 1588

Cenolate™ (Ascorbic Acid Injection, USP) is manufactured for Palatin Technologies, Inc. by Hospira, Chicago, IL 60064

Distributed by:

Mallinckrodt Inc.
St. Louis, MO 63134

Rx only

Printed in USA

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